Non-Hodgkin lymphoma

James O Armitage, Randy D Gascoyne, Matthew A Lunning, Franco Cavalli

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University of Nebraska Medical Center, Omaha, NE, USA (Prof J O Armitage MD, M A Lunning DO); **British Columbia Cancer Agency and British Columbia Cancer Research Centre, Vancouver, BC, Canada** (Prof R D Gascoyne MD); **and Oncology Institute of Southern Switzerland, Bellinzona, Switzerland** (Prof F Cavalli MD)

Correspondence to: Prof James O Armitage, University of Nebraska Medical Center, Nebraska Medical Center, Omaha, NE 68198-7680, USA
joarmita@unmc.edu

Lymphomas can affect any organ in the body, present with a wide range of symptoms, and be seen by primary care physicians and physicians from most specialties. They are traditionally divided into Hodgkin's lymphoma (which accounts for about 10% of all lymphomas) and non-Hodgkin lymphoma, which is the topic of this Seminar. Non-Hodgkin lymphoma represents a wide spectrum of illnesses that vary from the most indolent to the most aggressive malignancies. They arise from lymphocytes that are at various stages of development, and the characteristics of the specific lymphoma subtype reflect those of the cell from which they originated. Since this topic was last reviewed in *The Lancet* in 2012, advances in understanding the biology and genetics of non-Hodgkin lymphoma and the availability of new diagnostic methods and therapies have improved our ability to manage patients with this disorder.

Epidemiology and risk factors

Since the last review of non-Hodgkin lymphoma in *The Lancet* in 2012,[1] advances in understanding the biology and genetics and the availability of new diagnostic methods and therapies have improved. An estimated 72 580 new cases of non-Hodgkin lymphoma are expected in the USA in 2016, and 13 413 new cases were reported in the UK in 2013.[2,3] The relative frequency of specific subtypes of non-Hodgkin lymphoma varies geographically. The International Non-Hodgkin Lymphoma Classification Project[4] studied 4539 cases from seven geographical regions (North America, western Europe, southeastern Europe, Central and South America, north Africa and Middle East, southern Africa, and the east Asia). Non-Hodgkin lymphomas were more likely to be B-cell lymphomas, and there was a higher incidence of low-grade B-cell lymphomas in high-income regions than in low-income and middle-income regions. By contrast, low-income and middle-income regions had a higher incidence of high-grade B-cell lymphomas and T-cell and natural killer (NK)-cell lymphomas than did high-income regions. Nasal-type extranodal NK–T-cell lymphoma was much more common in the east Asia—and, to a lesser degree, in Central and South America—than in other regions. Extranodal NK–T-cell lymphoma is strongly associated with Epstein-Barr virus infection, but the striking geographical variability in the incidence of this subtype of lymphoma indicates a contribution of host susceptibility. However, one study[5] found that the distribution of lymphoma subtypes in Japan was changing and becoming more like the distribution found in the USA (ie, it was becoming westernised), suggesting that changes in lifestyle can alter these patterns.

Trends in the incidence of non-Hodgkin lymphoma have not been consistent. The incidence of non-Hodgkin lymphoma in Europe and North America increased in the 1990s and then stablised.[6,7] However, looking at overall trends of incidence might not reflect changes in the incidence of specific subtypes. For example, a study[8] from the Netherlands that focused on the period from 1989 to 2007 showed that the incidence of indolent B-cell lymphomas, and T-cell and NK-cell non-Hodgkin lymphomas, rose considerably whereas the incidence of aggressive B-cell lymphomas remained stable.

Factors affecting an individual's risk of developing non-Hodgkin lymphoma have been extensively studied. These factors include immune disorders, medicines, infections, lifestyle, genetics, race, family history, and occupational factors.[9–11] Obesity has been found to be a risk factor for diffuse large B-cell lymphoma (DLBCL).[12] Genome-wide association studies have found loci that are associated with excessive risk for follicular lymphoma, marginal zone lymphoma, and DLBCL.[13,14]

The effects of some key risk factors such as hair dyes seem to be decreasing owing to changes in the ingredients used in these products.[15] The risk of non-Hodgkin lymphoma in patients with autoimmune diseases—including rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus—has continued to increase.[16] Whether this increased risk is related only to the autoimmune disease or to the immunosuppressive therapies used in its management is not clear. Patients who are immunosuppressed for other reasons, such as patients undergoing organ transplantation or those with HIV infection, are known to be at an increased risk of developing non-Hodgkin lymphoma.[17]

Both viral and bacterial infections have been closely associated with the development of non-Hodgkin lymphomas. *Helicobacter pylori* causes most gastric mucosa-associated lymphoid tissue (MALT) lymphomas.[18] The Epstein-Barr virus is closely associated with both Burkitt lymphoma and nasal NK–T-cell lymphoma.[19,20] Hepatitis C virus has been associated with splenic marginal zone lymphoma and DLBCL.[21] *Borrelia burgdorferi* and *Chlamydia psittacosis* are thought to be

Search strategy and selection criteria

We searched PubMed and MEDLINE for articles published in English between Jan 1, 2012, and April 1, 2016, using the terms "non-Hodgkin lymphoma", "diffuse large B-cell lymphoma", "follicular lymphoma", "mantle cell lymphoma", "marginal zone lymphoma", "Burkitt lymphoma", "T-cell lymphoma" and "peripheral T-cell lymphoma". In some cases, these manuscripts provided further references that were not included in the original search results but were included in this manuscript.

associated with the development of marginal zone lymphomas,[22,23] and *Coxiella burnetii* has been proposed as a risk factor for DLBCL and follicular lymphoma.[24]

Sun exposure has been found to be protective against the development of non-Hodgkin lymphomas.[25] In one report[26] that used pooled databases, an association was found between cigarette smoking and the development of follicular lymphoma.[26] Some evidence indicates that alcohol intake might be protective against the development of non-Hodgkin lymphomas.[27] The risk factors identified for peripheral T-cell lymphomas, which are less frequent than other types of non-Hodgkin lymphoma, include coeliac disease, eczema, psoriasis, an extensive smoking history, and working with textiles or electricals.[28] In the same study,[28] individuals who consumed alcohol or had ever lived or worked on a farm were found to be protected from developing peripheral T-cell lymphomas.

Pathophysiology, genetics, and histopathology

Non-Hodgkin lymphoma includes a diverse spectrum of cancers of the immune system. About 85–90% of non-Hodgkin lymphomas are derived from B cells, whereas the remaining lymphomas are derived from T cells or NK cells. As of 2016, the current approach to classification uses the WHO classification scheme (panel 1). The 2016 revision builds on the 2008 WHO classification and incorporates information from clinical findings, morphology, immunophenotyping, and molecular genetics to refine previous entities that were considered to represent heterogeneous conditions, to describe new provisional entities on the basis of knowledge accrued during the intervening years, and to use new findings from next-generation sequencing studies that have provided substantial insight into disease biology (panel 1).[29] Recognition of the roles of age, anatomical site, and mutational profiles is reflected in the 2016 revision, as is additional clarity surrounding so-called early lesions, which are seen in both follicular lymphoma and mantle cell lymphoma. The 2016 revision also adds additional clarity regarding the borderline lesions described in 2008, such as the lesions in mediastinal grey zone lymphomas, the features of which overlap with nodular sclerosis Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. Further refinements to the WHO classification scheme can be expected as fundamental improvements in our understanding are achieved through clinical, translational, and basic science research studies. Importantly, two specific lymphomas, follicular lymphoma and DLBCL, account for about 65% of all non-Hodgkin lymphomas, and thus a thorough knowledge of these two entities is essential.

The gene-expression profiles of almost all non-Hodgkin lymphomas are a reflection of the equivalent healthy cell of origin from which the lymphoma is derived, but they also reflect changes that result from recurrent genetic, epigenetic, and other molecular alterations (eg, copy-number gains

Panel 1: **Classification of non-Hodgkin lymphoma subtypes***

Mature B-cell neoplasms

- Chronic lymphocytic leukaemia and small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- Unclassifiable splenic B-cell lymphoma or leukaemia†
- Splenic diffuse red pulp small B-cell lymphoma†
- Hairy cell leukaemia variant
- Lymphoplasmacytic lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
- Nodal marginal zone lymphoma
- Paediatric nodal marginal zone lymphoma†
- Follicular lymphoma
- In-situ follicular neoplasia
- Paediatric-type follicular lymphoma
- Large B-cell lymphoma with rearrangement of *IRF4*†
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- In-situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
- T-cell-rich or histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Leg-type primary cutaneous DLBCL
- Epstein-Barr virus (EBV)-positive DLBCL, not otherwise specified
- EBV-positive mucocutaneous ulcer†
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Human herpesvirus 8-positive DLBCL, not otherwise specified†
- Burkitt lymphoma
- Burkitt-like lymphoma with chromosome 11q aberrations†
- High-grade B-cell lymphoma with rearrangements of *BCL2* and *MYC* or of *BCL6* and *MYC*†
- High-grade B-cell lymphoma, not otherwise specified†
- Unclassifiable B-cell lymphoma with features that are intermediate between DLBCL and classic Hodgkin's lymphoma

Mature T-cell and natural killer (NK)-cell neoplasms

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia

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(Panel 1 continued from previous page)

- Chronic lymphoproliferative disorder of NK cells†
- Aggressive NK-cell leukaemia†
- EBV-positive T-cell lymphoproliferative diseases of childhood, including cutaneous chronic active EBV infection, hydroa vacciniforme-like lymphoma, severe mosquito-bite hypersensitivity, systemic chronic active EBV infection, and systemic EBV-positive T-cell lymphoma of childhood
- Adult T-cell leukaemia or lymphoma
- Nasal-type extranodal NK–T-cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract†
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma†
- Primary cutaneous acral CD8-positive T-cell lymphoma†
- Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder†
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma†
- ALK-positive anaplastic large cell lymphoma
- ALK-negative anaplastic large cell lymphoma
- Breast implant-associated anaplastic large cell lymphoma†

*Plasma cell neoplasms, Hodgkin's lymphomas, post-transplant lymphoproliferative disorders, and tumours of histiocytic and antigen-presenting cells are not included in this panel. †Provisional entities.

and losses); such changes affect the transcriptome and ultimately the proteome.[30] B-cell non-Hodgkin lymphoma is a paradigm of translocation-based cancers in which deregulated gene expression occurs as a result of characteristic balanced translocations that place key genes under the influence of active lineage-specific promoters or enhancers. For example, the immunoglobulin heavy chain (IGH) locus on chromosome 14q32 is actively transcribed in B cells because these cells require the expression of a B-cell receptor on the cell surface for their survival. Follicular lymphoma most commonly results from the t(14;18)(q32;q21) translocation; this translocation places BCL2 (which encodes B-cell CLL/lymphoma 2) under control of the IGH enhancer element, leading to constitutive BCL2 expression. BCL-2 is an anti-apoptotic protein, and the t(14;18)(q32;q21) translocation results in markedly elevated expression of BCL-2, which blocks the healthy germinal centre default programme of apoptotic cell death and represents a defining pathogenic feature of follicular lymphoma.[31] Similarly, mantle cell lymphoma is characterised by the t(11;14)(q13;q32) translocation, which leads to the deregulated expression of cyclin D1, and Burkitt lymphoma overexpresses MYC as a result of the t(8;14)(q24;q32) translocation or variants. Other translocations define additional subtypes of both B-cell and T-cell lymphomas.

Healthy B cells begin their lives in the bone marrow, where they undergo rearrangement of their immunoglobulin gene segments before antigen encounter. These naive B cells exit the bone marrow to seed secondary lymphoid organs such as the lymph nodes and spleen. Here they encounter antigen and, with the help of T cells, form primary and subsequently secondary lymphoid follicles, the latter of which are characterised by germinal centres. Healthy germinal centres represent sites of affinity maturation, a process that results in the selection of B cells that secrete high-affinity antibodies. The germinal centre is a unique physiological structure, that supports rapid B-cell proliferation and also two physiological genetic processes, known as somatic hypermutation (SHM) and class-switch recombination, which both require double-stranded DNA breaks.[23] The ability of germinal centres to support these processes is potentially lethal because although these processes are required for the generation of antibody diversity, they are also error-prone and probably underlie lymphomagenesis.[23] The presence of somatically hypermutated immunoglobulin genes both in healthy and malignant B cells is a footprint of germinal centre transit and is used to characterise most B-cell non-Hodgkin lymphomas according to the stages of differentiation that occur in germinal centres. For example, about 40% of chronic lymphocytic leukaemias and a proportion of mantle cell lymphomas have transited the germinal centre.[32] The rapid cell turnover and DNA damage that occur within the healthy germinal centre are controlled by a series of carefully controlled transcription factors including BCL-6, MYC, and PRDM1, for example.[23] Not surprisingly, somatically acquired genetic alterations of these and other B-cell differentiation factors directly lead to the development of lymphoma.[33]

Less is known about mature or so-called peripheral T-cell lymphomas. Classification of these lymphomas uses a framework that is based on the distinction between lymphocytes of the innate immune system (NK cells and γδ T cells), which are not antigen specific, versus those of the adaptive immune system (mature CD4-positive and CD8-positive αβ T cells, and regulatory T cells), which are antigen specific.[34] The classification of T-cell non-Hodgkin lymphomas is complex (panel 1), and many of the recognised distinct entities are frequently characterised by relatively specific clinical features, morphological

aspects, immunophenotypes, and recurrent genetic alterations.[22] Recurrent translocations are less common in peripheral T-cell lymphomas than in other types of lymphoma, and examples include the characteristic t(2;5)(p23;q35) translocation seen in anaplastic lymphoma kinase (ALK)-positive anaplastic T-cell lymphoma and the t(5;9)(q33;q22) translocation associated with follicular T-cell lymphoma.[27] In 2016, ALK-negative anaplastic T-cell lymphoma will change from being a provisional entity to an accepted lymphoma entity, and it represents a paradigm of how progress in understanding disease biology translates into improved classification schemes. Next-generation sequencing studies are helping to resolve both the clinical and biological heterogeneity of this disease entity, as recurrent translocations including t(6;7)(p25;q32) and recurrent gene fusions involving the tumour-suppressor gene *TP63* characterise subsets of ALK-negative anaplastic T-cell lymphoma that are associated with strikingly different survival rates.[35]

Some common themes related to pathogenesis of non-Hodgkin lymphoma have begun to emerge owing, in part, to knowledge acquired through gene-expression profiling and next-generation sequencing.[36,37] For example, node-based DLBCL comprises two major molecular subtypes of disease that are referred to as the germinal centre B-cell subtype and the activated B-cell subtype.[29] These two subtypes of DLBCL are essentially different entities and are characterised by differences in survival, disease biology, gene expression, and specific oncogenic pathway perturbations, the latter of which are being used to inform novel therapeutic approaches.[38] Similar methodological approaches are being used to inform precision medicine across the spectrum of non-Hodgkin lymphoma, and will be a major focus of future clinical and translational research. Common themes underpinning lymphoma biology include (1) genetic alterations that promote growth and survival (eg, mutations in CDKN2A that alter cell-cycle control, mutations affecting JAK–STAT signalling); (2) constitutive upregulation of key signalling pathways (eg, those involving CD79B, MYD88, CARD11); (3) inhibition of apoptosis (eg, upregulation of BCL2 by translocation or copy-number gain); (4) blocks to terminal differentiation (eg, BCL6 translocations and loss of PRDM1); (5) immune escape (eg, translocations of PDL1, and mutations involving CD58 or B2M); and (6) global alterations of genes that are involved in chromatin remodelling and histone modification (eg, mutations involving EZH2, CREBBP, EP300, KMT2D).[23] The latter appear to be common to both B-cell and T-cell lymphomas, and were largely unrecognised until next-generation sequencing studies were completed.[30]

Clinical presentation, staging, and restaging

Most patients with non-Hodgkin lymphoma present with painless lymphadenopathy, and might or might not have systemic symptoms such as fevers, drenching night sweats, weight loss, pruritis, and fatigue. However, since non-Hodgkin lymphoma can involve any organ in the body, a myriad of presentations are possible, and symptoms might mimic a wide range of other conditions. Diagnosis should be based on an adequate biopsy sample reviewed by an experienced haematopathologist. Preferably this sample will be from an excisional biopsy of an involved lymph node or a tumour in another organ, but a cutting-needle biopsy is sometimes the only practical choice. The diagnosis of non-Hodgkin lymphoma using fine-needle aspiration or cytology from an effusion should be avoided. Obtaining a sufficient amount of tissue to enable immunohistochemical studies and genetic studies will increase the chance of a pathologist reaching the correct diagnosis. The differential diagnosis of the many subtypes of non-Hodgkin lymphoma is broad and varies for each specific subtype (table 1).

Following a definite diagnosis, staging should be done and should include (1) careful history taking and physical examination; (2) laboratory studies to assess the function of the bone marrow and other organs, and measurement of serum concentrations of lactate dehydrogenase; and (3) imaging studies. As recommended in the Lugano classification, both CT and PET scans can provide important information, but combined PET–CT is

	Conditions included in the differential diagnosis
Lymphoblastic lymphoma	Mediastinal cases might in fact be benign with the tumours comprising healthy cortical thymocytes; Burkitt lymphoma; Burkitt-like lymphoma; blastoid mantle cell lymphoma; myeloid sarcoma
Diffuse large B-cell lymphoma	Peripheral T-cell lymphoma; Burkitt-like lymphoma; lymphoblastic lymphoma; grade 3B follicular lymphoma; myeloid sarcoma; carcinoma; melanoma
Follicular lymphoma	Follicular hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; mantle cell lymphoma; marginal zone lymphoma; lymphoplasmacytic lymphoma; nodular lymphocyte-predominant Hodgkin's lymphoma; lymphocyte-rich classic Hodgkin's lymphoma
Mantle-cell lymphoma	Reactive hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; grade 1 and 2 follicular lymphomas; lymphoplasmacytic lymphoma; nodular lymphocyte-predominant Hodgkin's lymphoma; lymphocyte-rich classic Hodgkin's lymphoma
Small lymphocytic lymphoma	Reactive hyperplasia; mantle cell lymphoma; diffuse follicular lymphoma; marginal zone lymphoma; lymphoplasmacytic lymphoma; nodular lymphocyte-predominant Hodgkin's lymphoma; lymphocyte-rich classic Hodgkin's lymphoma
Mucosa-associated lymphoid tissue lymphoma	Reactive hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; follicular lymphoma (particularly those with marginal zone differentiation); nodal and splenic marginal zone lymphomas; lymphoplasmacytic lymphoma
Nodal marginal zone lymphoma	Reactive hyperplasia; small lymphocytic lymphoma; chronic lymphocytic leukaemia; follicular lymphoma (particularly those with marginal zone differentiation); nodal and splenic marginal zone lymphomas; lymphoplasmacytic lymphoma; nodular lymphocyte-predominant Hodgkin's lymphoma; lymphocyte-rich classic Hodgkin's lymphoma
Splenic marginal zone lymphoma	Marginal zone hyperplasia in the spleen; mantle-cell lymphoma in the spleen; follicular lymphoma in the spleen; small lymphocytic lymphoma; chronic lymphocytic leukaemia; lymphoplasmacytic lymphoma; hairy cell leukemia and variants
Burkitt lymphoma	Burkitt-like lymphoma; diffuse large B-cell lymphoma; blastoid mantle cell lymphoma; lymphoblastic lymphoma; myeloid sarcoma
Peripheral T-cell lymphoma, not otherwise specified	Florid reactive hyperplasia; T-cell-rich diffuse large B-cell lymphoma; mixed cellularity Hodgkin's lymphoma

Table 1: **Differential diagnosis of selected subtypes of non-Hodgkin lymphoma**

Panel 2: The International Prognostic Index

The International Prognostic Index is calculated for all patients (a score of 0–5) and patients aged 60 years or younger (a score of 0–3) by summing the following risk factors.

Risk factors in all patients

- Older than 60 years
- Serum lactate dehydrogenase concentrations higher than the highest normal value
- ECOG performance state
- Stage 3 or 4
- Extranodal involvement in two or more sites

Risk factors in patients aged 60 years or younger

- Serum lactate dehydrogenase concentrations higher than the maximum normal value
- ECOG performance state
- Stage 3 or 4

	Criteria
1	No uptake related to lymphoma
2	The highest uptake in any site of lymphoma is less than or equal to to the uptake by the mediastinum
3	The highest uptake by any site of lymphoma is greater than the uptake by the mediastinum, but less than or equal to the uptake by the liver
4	The uptake by any site of lymphoma is greater than the uptake by the liver
5	The presence of new sites of uptake or substantial increases in the standardised uptake value in previous sites of lymphoma, or both

Table 2: **The Deauville score for assessing PET–CT scans to measure patient responses to therapy**

generally the most useful imaging modality.[39] The absence of abnormal metabolic activity in a suspicious site on a CT scan, or the presence of abnormal metabolic activity at a site that was not abnormal on the CT scan, can reduce or increase the stage of a patient's disease, respectively. Additionally, PET–CT scans appear to be as sensitive as bone-marrow biopsy in identifying bone-marrow involvement in some subtypes of non-Hodgkin lymphoma, including DLBCL.[40,41] Bone-marrow biopsy remains preferable for identifying bone-marrow involvement in more indolent lymphomas such as follicular lymphoma.

Several systems for predicting prognosis and making a treatment recommendation have been developed and are widely used. The first of these systems was the International Prognostic Index (IPI; panel 2),[42] which was developed for aggressive B-cell and T-cell lymphomas, but is predictive in essentially all subtypes of non-Hodgkin lymphoma. Modification of the IPI for DLBCL seems to improve its predictive value.[43] Other systems exist, sometimes with several iterations, for follicular lymphoma,[44] mantle cell lymphoma,[45] and peripheral T-cell lymphoma.[46]

The end-of-treatment PET–CT scan is the best predictor of disease-free survival and has become a standard definition of complete remission,[47] at least in the aggressive lymphomas and follicular lymphoma. The establishment of this standard definition was made possible by the development of the Deauville score (also known as the five-point score; table 2).[48] Studies in DLBCL and follicular lymphoma have shown that a score of less than or equal to three predicts a good treatment outcome and should be the definition of complete remission.[47,49]

Repeated staging studies after one-to-three cycles of chemotherapy (often called interim restaging) is sometimes used to guide treatment decisions, including the decision to lengthen or shorten the duration of therapy, to intensify therapy, or to change treatments. However, changing therapy on the basis of the interim PET–CT scan is not recommended in the National Comprehensive Cancer Network guidelines.[50] The interpretation of an interim PET–CT scan is complicated because PET scans are very sensitive and a negative scan has a high predictive value, whereas a positive scan has a lower predictive value. An interim scan is often considered to be negative with a Deauville score of less than or equal to two, which is more stringent than the cutoff for end-of-treatment scans. Notably, some patients with a positive interim scan will be cured by continuing on the same treatment.[51]

Management of specific subtypes of non-Hodgkin lymphoma

Precursor B-cell and T-cell lymphomas

Lymphoblastic lymphoma can be of pre-B-cell or pre-T-cell origin, and it represents the same disease as acute lymphoblastic leukaemia presenting as a solid tumour. Precursor T-lymphoblastic leukaemia typically presents as a mediastinal mass in young men, whereas precursor B-lymphoblastic lymphoma is more likely to involve the lymph nodes, skin, and bone. Both of these neoplasms are rapidly progressive and have a tendency to spread to the central nervous system (CNS). Patients are usually managed with regimens that were developed for acute lymphoblastic leukaemia. For patients who are young and healthy enough to tolerate them, the very intensive regimens typically used in children seem to be the most effective.[52]

Mature B-cell and T-cell lymphomas

DLBCL

DLBCL is the most common subtype of non-Hodgkin lymphoma. The most important advance in the management of DLBCL in the past two decades was the recognition that the addition of rituximab to an anthracycline-containing chemotherapy regimen significantly improves treatment results both in prospective randomised trials and in observational studies in defined populations.[53,54] The regimen including cyclophosphamide, doxorubicin, vincristine, prednisone,

and rituximab (known as CHOP-R) administered every 3 weeks has been the standard treatment for DLBCL in most of the world. However, some studies indicate that more intensive regimens might improve the outcome in young patients who are able to tolerate such therapy. For example, the Groupe d'Etudes des Lymphomes de l'Adulte[55] has reported that doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, and rituximab (ACVBP-R) is superior to CHOP-R in young patients (3 year progression-free survival 87% *vs* 73%) with DLBCL. Similarly, phase 2 trials in the USA[56] have indicated that the infusional chemotherapy regimen including etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R) might be superior to CHOP-R, and the results of a large intergroup study are anticipated soon.

Patients with localised DLBCL are occasionally cured by radiotherapy alone, but these patients have the best outcome when they receive chemotherapy as part of their initial treatment. Frequently, chemotherapy—sometimes with a reduced number of cycles—is followed by radiotherapy, but chemotherapy alone can cure most patients.[57] A very large mass and bone involvement have traditionally been indications for radiotherapy following chemotherapy, but the use of PET scanning has raised the question of whether radiotherapy is necessary for patients who have a negative PET scan after chemotherapy. Patients who complete a course of chemotherapy and have a negative PET scan seem to be cured without requiring consolidative radiotherapy, even if the original tumour was large.[58] Patients with localised DLBCL have an excellent outcome, and the long-term survival (ie, 5–10 years) of patients in most series is more than 80%. Other prognostic factors, such as the distinction between germinal centre B-cell and activated B-cell subtypes, seem to be less important.[59]

DLBCLs originating in germinal centre B cells have a better prognosis than DLBCLs originating from activated B cells that have exited the germinal centres.[60] The addition of rituximab to standard chemotherapy regimens improves the outcome of both the germinal centre B-cell and activated B-cell subtypes of DLBCL, but it does not eliminate the disadvantage of having the activated B-cell subtype. Attempts to improve the outcome of patients with the activated B-cell subtype type of DLBCL have included the use of the infusional regimen EPOCH-R,[61] very intensive regimens such as ACVBP-R,[62] and the addition of other drugs to CHOP-R, such as lenalidomide.[63] CNS prophylaxis, often with intrathecal methotrexate, is frequently given to patients who are at a high risk of CNS relapse.[64,65]

Lymphomas with mutations involving both MYC and either BCL2 or BCL6 have been referred to as double-hit lymphomas. They are most frequently seen in patients with lymphomas that are at the interface between DLBCL and Burkitt lymphoma, but some DLBCLs fit into this category.[66] DLBCLs with MYC and BCL2 mutations are of germinal centre B-cell origin, and those with MYC and BCL6 are often of activated B-cell origin.[67] DLBCLs with these mutations respond poorly to standard chemotherapy regimens, have a lower incidence of complete remission, and frequently progress during therapy.[66,67] Patients are often given autologous haemopoietic stem cell transplants when they are in complete remission, but whether this improves the outcome is unknown because patients who achieve complete remission are sometimes cured without requiring further therapy.[68] Lymphomas that overexpress the proteins BCL-2 and MYC but do not have translocations in the respective genes have been referred to as double expressors; they are usually of activated B-cell origin and have a poor outcome.[69] However, the outcome is intermediate between double-hit DLBCLs and DLBCLs that are neither double-hit nor double expressors.

Patients who present with a very high IPI score do less well than patients with fewer adverse prognostic factors.[70] A large intergroup study from the USA found that patients with a very high IPI score had a significantly improved outcome when they received autologous haemopoietic stem-cell transplantation during their first remission.[71] One fairly consistent risk factor has been male sex. Studies have shown that men metabolise rituximab faster than do women[72] and that this difference in metabolism might partially explain the poorer outcome in men given rituximab-containing regimens. A German study reported that the use of intensified rituximab treatment in males seemed to eliminate the sex disadvantage.[73]

DLBCLs arising in extranodal sites can have unique clinical features. For example, primary mediastinal lymphoma is seen more often in young women than in other individuals, and it spreads to other extranodal sites.[29] With CHOP-R and radiotherapy, most patients are cured,[74] but a negative PET scan at the end of chemotherapy can make routine radiotherapy unnecessary.[75] In one study of EPOCH-R without radiotherapy, event-free survival was reported to be 93%.[76] Primary CNS DLBCL can sometimes be cured by chemotherapy regimens that include high-dose methotrexate, and radiotherapy is not always necessary.[77]

Patients with DLBCL who relapse after achieving complete remission or who do not achieve complete remission with their initial regimen have a poor prognosis, but some of these patients can be cured if they receive an autologous haemopoietic stem-cell transplant after responding to a salvage chemotherapy regimen.[78] Evidence indicates that the benefit of autologous transplantation is less in patients who have rituximab in their initial chemotherapy regimen than in those patients whose initial regimen does not include rituximab,[79] but autologous transplantation still represents the most likely chance for a cure after relapse.[80] Patients who do not respond to an autologous transplant can occasionally be cured by an allogeneic transplant.[81] Chimeric antigen

receptor T cells are active in patients with refractory DLBCL.[82] Patients who have relapsed and have the activated B-cell subtype of DLBCL, but not the germinal centre B-cell subtype, often respond to the B-cell receptor inhibitor ibrutinib.[38]

Follicular lymphoma

Follicular lymphoma is divided into three grades according to the number of large transformed cells in the tumour.[22] The WHO classification of follicular lymphoma subdivides grade 3 into lymphomas that are expected to behave more like DLBCL—ie, grade 3B follicular lymphomas, which have sheets of centroblasts—and those referred to as grade 3A follicular lymphomas (in which most of the large cells are centrocytes). The WHO classification recommends that grade 3B follicular lymphomas should be treated in the same way as DLBCL, whereas grade 3A follicular lymphomas should be treated in the same way as low-grade follicular lymphoma. The survival of patients with low-grade follicular lymphoma was about 10 years before the availability of monoclonal antibodies such as rituximab.[83,84] However, the duration of survival has now improved to a median of 15 years or more.[85–87] Even so, patients who relapse in the first 1–2 years continue to have a poorer survival than patients who relapse later, and early-relapsing patients might require a different treatment approach;[88] prospective identification of these patients could thus be useful. Most patients with follicular lymphoma have disseminated disease, but radiotherapy has frequently been used in the rare patients with stage 1 follicular lymphoma, and the 10-year relapse-free survival rates have averaged about 50%.[89] For patients who are asymptomatic at the time of diagnosis, and are comfortable at being observed without therapy, no evidence exists to indicate that a so-called watch and wait approach reduces survival.[90] A watch and wait approach is often recommended in treatment guidelines both in the USA and in Europe.[91,92] However, most patients will eventually require systemic therapy. Single-agent rituximab, often with maintenance rituximab, had a high response rate in a prospective trial from the UK in which 88% of the patients who received rituximab followed by maintenance rituximab did not require a new treatment at 3 years, and the overall survival at 3 years was 97%.[93] For patients with more bulky disease, and for those who require a rapid response to therapy because of specific symptoms or life-threatening manifestations of their lymphoma, initial treatment is usually with a regimen that combines traditional chemotherapy drugs with rituximab. Although many regimens are used, the two most popular regimens in North America are bendamustine plus rituximab and CHOP-R.[94,95] Additionally, chlorambucil plus rituximab is sometimes used, and the combination of lenalidomide and rituximab looks promising.[96] Whether any one of these treatment approaches is definitely superior to the others is unclear. Whatever the initial chemotherapy regimen, maintenance rituximab clearly extends remission, but no evidence clearly indicates that it improves overall survival.[95]

For patients with relapsed follicular lymphoma, both autologous haemopoietic stem-cell transplantation[97,98] and allogeneic haemopoietic stem-cell transplantation[99] can yield long-lasting freedom from relapse and a potential cure, and patients transplanted after their first or second relapse have a better prognosis than do patients transplanted later in the course of their illness.[100] A range of new treatment approaches are available for patients with relapsed follicular lymphoma, including idelisilib and ibrutinib, which target the B-cell receptor pathway,[101] lenalidomide,[96] the BCL-2 inhibitor venetoclax,[102] and inhibitors of programmed cell death protein 1 (PD1) or PD1 ligand 1 (PDL1).[103]

Mantle cell lymphoma

Since the recognition of mantle cell lymphoma as a distinct entity in the 1990s, the survival of patients with this condition has considerably improved.[104] A subset of patients with mantle-cell lymphoma who present with blood and bone-marrow involvement, and an enlarged spleen, can have an unusually indolent course and can be observed without therapy.[105] Most patients with mantle-cell lymphoma require therapy soon after diagnosis. CHOP-R is clearly not a sufficiently active regimen for this disease.[106] Common approaches to the treatment of this type of lymphoma include CHOP in which bortezomib is used instead of vincristine,[107] bendamustine plus rituximab,[108] and various regimens including high-dose cytarabine.[109,110] Additionally, new treatment approaches are being developed that involve more novel drugs, including the combination of lenalidomide plus rituximab—which achieved a 2-year progression-free survival rate of 85%—and a combination of ibrutinib with bendamustine and rituximab.[111,112] As in patients with follicular lymphoma, maintenance rituximab seems to extend remission in patients with mantle-cell lymphoma and is frequently used.[113] Autologous haemopoietic stem-cell transplantation during the first remission is often incorporated as part of the initial regimen.[114] Patients who relapse sometimes respond to lenalidomide, ibrutinib, and bortezomib or bendamustine plus rituximab.[115–118]

Marginal zone lymphoma

Marginal zone lymphomas are divided into MALT lymphomas, nodal marginal zone lymphomas, and splenic marginal zone lymphomas. MALT lymphomas are the most frequent, and the most common site of presentation is the stomach. Patients with gastric MALT lymphoma are almost always infected with *Helicobacter pylori*, and eradication of the infection will often lead to a clinical remission.[119] However, the presence of the t(11;18) translocation predicts a higher chance of not

achieving remission and an increased risk of relapse.[120] For patients with localised gastric MALT lymphoma who do not achieve complete remission following antibiotic use, radiotherapy is usually curative.[121] For advanced MALT lymphoma, chemotherapy plus rituximab is superior to the use of either treatment alone.[94] Patients with nodal marginal zone lymphoma are usually given chemotherapy, monoclonal antibodies, or the combination of these agents in a similar manner to the treatment of low-grade follicular lymphoma. Splenic marginal zone lymphoma typically presents with splenomegaly, and blood and bone-marrow involvement, but no lymphadenopathy. Patients with concomitant hepatitis C virus infection might respond to eradication of the virus.[122] For other patients with symptomatic disease, either single-agent rituximab or splenectomy can lead to clinical remission and extended survival.[123,124]

Small lymphocytic lymphoma and chronic lymphocytic leukaemia

Small lymphocytic lymphoma and chronic lymphocytic leukaemia represent different presentations of one illness; the diagnosis of small lymphocytic lymphoma is made in patients who present primarily with lymphadenopathy or hepatosplenomegaly.[22] The same treatment approaches used in chronic lymphocytic leukaemia are also typically used in patients diagnosed with small lymphocytic lymphoma, and the recent addition of new drugs has substantially improved treatment results.[125] Recent reports[82] indicate that chimeric antigen receptor T-cell therapy can induce durable remission in patients with refractory disease.

Burkitt lymphoma

Burkitt lymphoma is perhaps the most rapidly proliferating human malignancy, and because the disease can progress so rapidly and has a tendency to disseminate to the CNS, a timely diagnosis and the prompt institution of effective therapy are important. CNS prophylactic therapy must be included in any treatment regimen. Very intensive short-course regimens without maintenance therapy or the incorporation of bone-marrow transplantation can cure most patients. Studies report an 80–90% survival rate among adults with Burkitt lymphoma who are given popular regimens such as CODOX-M-IVAC (the combination of cyclophosphamide, vincristine, doxorubicin, and methotrexate with etoposide, ifosfamide, and cytarabine),[126] hyper CVAD (the combination of cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine),[127] and other similar regimens.[128] The addition of rituximab to treatment regimens appears to improve the outcome.[129] The survival rate among adults with Burkitt lymphoma who are given the infusional chemotherapy regimen EPOCH-R is more than 90%, and this regimen appears to be more tolerable than are previous intensive regimens.[130] The German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia used a modified regimen that was better tolerated in older patients than was the previous regimen, and they reported a 60% 5-year progression-free survival in patients with Burkitt lymphoma older than 55 years.[131] Patients who do not respond to an intensive regimen are rarely cured.[132]

Peripheral T-cell lymphomas

Mature T-cell lymphomas, such as peripheral T-cell lymphomas, are much less common than their B-cell counterparts but have as many subgroups, which makes clinical trials difficult and means that treatment guidelines are more based on expert opinion than on the results of randomised trials.[133,134] Most indolent peripheral T-cell lymphomas involve the skin; these lymphomas include mycosis fungoides, cutaneous anaplastic large T-cell lymphoma, lymphomatoid papulosis, and other less common entities. In this section, we focus on the management of the aggressive peripheral T-cell lymphomas. In most series of patients, peripheral T-cell lymphoma not otherwise specified remains the most common subtype of aggressive peripheral T-cell lymphoma, although gene profiling of these tumours is enabling better characterisation of disease entities and the identification of new subtypes.[135] Accurate diagnosis remains an issue in the care of patients with peripheral T-cell lymphomas, and in a large series of patients who were referred to academic medical centres, the original diagnosis was changed in about a third of cases, which often led to a change in disease management.[136] No standard therapy exists for patients with peripheral T-cell lymphoma not otherwise specified. These patients have traditionally received regimens such as CHOP and often receive an autologous haemopoietic stem-cell transplant during remission, and some patients are cured. However, some studies have not shown a definite benefit from the incorporation of an anthracycline in the treatment regimen for patients with peripheral T-cell lymphoma.[137] Several studies have shown an apparent benefit to autologous haemopoietic stem cell transplantation during remission.[138] Analysis of real-world data from the Swedish Lymphoma Registry showed superior progression-free survival (hazard ratio 0·56; p=0·002) among patients undergoing autologous haemopoietic stem-cell transplantation in first remission compared with those not receiving autologous haemopoietic stem-cell transplantation.[139]

Specific subtypes of peripheral T-cell lymphoma seem to benefit from particular regimens. For example, patients with anaplastic large T-cell lymphoma have the best outcome with an anthracycline-containing regimen such as CHOP or CHOP plus etoposide. Patients with ALK-positive anaplastic T-cell lymphoma have a better outcome than those with ALK-negative anaplastic T-cell lymphoma, but this improved outcome is at least partly

age related, and older patients with either ALK-positive or ALK-negative anaplastic T-cell lymphoma seem to have approximately the same outcome.[140,141] Patients with localised extranodal NK–T-cell lymphoma presenting in the nose or nasal sinuses can be cured in more than 50% of instances when radiotherapy is included in the treatment regimen.[142] These patients seem to be particularly sensitive to chemotherapy regimens that include L-asparaginase.[143]

A range of new treatment approaches are showing promise in peripheral T-cell lymphoma. Peripheral T-cell lymphomas expressing CD30 (CD30 expression is found in all patients with anaplastic T-cell lymphoma) are likely to respond to the antibody conjugate brentuximab vedotin.[144] Brentuximab vedotin is now being incorporated into front-line regimens and usually substitutes for vincristine in the CHOP regimen. ALK-positive anaplastic T-cell lymphoma can also respond to the ALK inhibitor crizotinib.[145] Other chemotherapeutic agents such as pralatrexate, romidepsin, belinostat, and alisertib all have activity in peripheral T-cell lymphomas and can be used in patients with relapsed or refractory disease.[146–148]

Long-term follow-up

Survivorship issues are particularly important in a disease in which patients survive for a long time and can frequently be cured. These issues include screening for, and prevention of, additional cancers and cardiovascular disease, and recognising and managing depression, fatigue, infertility, work loss, and sexual dysfunction. Guidelines for caring for survivors are being developed. These tasks will fall to primary care physicians and oncologists.

In many parts of the world, surveillance imaging in patients who are in complete remission has been routine for patients with non-Hodgkin lymphoma. In part, the use of surveillance imaging has been driven by the existence of effective salvage therapy, including the potential for cure with bone-marrow transplantation. However, no studies have proven that surveillance imaging can improve survival. One study from French and American centres analysed surveillance imaging in patients with DLBCL who had achieved complete remission with standard therapy and found that 20% of patients relapsed.[149] Most of the patients who had relapsed were not identified at the time of a routine follow-up visit, and surveillance uniquely detected relapse in less than 2% of patients.[149] A study[150] compared the outcomes for patients in complete remission from DLBCL from Denmark (ie, where routine surveillance imaging was done) with the outcomes of those from Sweden (where no routine surveillance imaging was done). Both countries otherwise used similar follow-up intervals and studies. The survival of patients was not different between these groups, and the authors suggested that the money being spent on imaging might be better used to address survivorship issues.

Controversies and research questions

The post-treatment PET–CT scan has had a major impact on the definition of complete remission. However, the place of the interim PET–CT scan remains to be defined in non-Hodgkin lymphoma. PET–CT could possibly improve treatment outcomes by identifying non-responders early, and thus enabling therapy to be changed accordingly, and by allowing treatment intensity to be reduced, thus avoiding toxicity in patients who show a rapid response to treatment.

The biggest challenge is the integration of the huge amount of genetic information provided by genomic studies into useful tools for the diagnosis and therapeutic management of lymphomas of all subtypes, but particularly DLBCL; the definition of which treatment is best for each of the genetic subgroups of DLBCL is important for randomised trials (some of which are ongoing).

The findings from the US Intergroup Study comparing the infusional regimen EPOCH-R with CHOP-R in patients with DLBCL should be reported soon. If some patients benefit from a more intensive regimen, the results of this study could change current practice. Additionally, ongoing clinical trials are studying the use of B-cell receptor inhibitors, lenalidomide, and new anti-CD20 antibodies in the activated B-cell subtype of DLBCL, follicular lymphoma, and mantle cell lymphoma. Once again, if the findings of these studies are positive, they could change standard treatment approaches. Although rituximab has been in general use for more than a decade and a half, the best way to use this drug is still uncertain. The optimal dose is unclear, particularly in elderly men. The use of maintenance rituximab in treating indolent lymphomas is still debated.

Peripheral T-cell lymphoma remains the least well understood form of non-Hodgkin lymphoma. The relative infrequency of peripheral T-cell lymphomas makes clinical trials difficult, and our understanding of the biology of these lymphomas is far less well understood than that of B-cell non-Hodgkin lymphoma. A better definition of standard chemotherapy regimens is badly needed. These regimens will probably be quite different from the standard treatment approaches used for B-cell non-Hodgkin lymphoma.

Finally, survivorship issues need to be seriously addressed. These issues include identifying the best way to follow up patients and monitor for recurrence, developing measures to prevent late treatment complications, such as additional cancers and cardiovascular disease, and addressing other problems such as fatigue, depression, and underemployment.

Conclusion

Our understanding of the biology of non-Hodgkin lymphoma, particularly B-cell non-Hodgkin lymphoma, has greatly improved. The existence of so-called pre-lymphoma or early lesions in non-Hodgkin lymphoma—which are analogous to monoclonal B lymphocytosis

in chronic lymphocytic leukaemia and monoclonal gammopathy of unknown significance in myeloma—are now recognised. Investigation of the genetic abnormalities that underlie non-Hodgkin lymphomas is providing targets for the development of new treatments. PET–CT scanning is the best predictor of a good treatment outcome in most of the common subtypes of non-Hodgkin lymphoma. An increasing amount of evidence indicates that DLBCL consists of many subtypes that are not all optimally treated by one approach. The overall survival for patients with low-grade follicular lymphoma and mantle-cell lymphoma has increased considerably in the past one-to-two decades, and the combination of an anti-CD20 antibody with new agents such as lenalidomide or ibrutinib might simplify therapy. The next *Lancet* Seminar on non-Hodgkin lymphoma will probably summarise even more striking changes in our understanding of these disorders and discuss considerably better treatment outcomes.

Contributors

All authors participated in writing the manuscript.

Declaration of interests

JOA is a consultant for Conatus IDMC and Ziopharm, and is a member of the board of directors for Tesaro. RDG is a consultant for Seattle Genetics and Celgene. MAL is a consultant for AbbVie and Seattle Genetics, and is a member of the advisory boards for Bristol-Myers Squibb, Celgene, Genentech, Gilead Sciences, Juno Therapeutics, Pharmacyclics, TG Therapeutics, and Jazz Pharmaceuticals. FC declares no competing interests.

References

1 Shankland KR, Armitage JO, Hancock DW. Non-Hodgkin lymphoma. *Lancet* 2012; **380:** 848–75.

2 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2016. CA *Cancer J Clin* 2016; **66:** 7–30.

3 Cancer Research UK. Non-Hodgkin lymphoma incidence statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence (accessed June 29, 2016).

4 Perry AM, Jacque D, Nathwani BN, et al. Classification of non-Hodgkin lymphoma in seven geographic regions around the world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project, ASH abst#1484. *Blood* 2015; **126:** 1484 (abstr).

5 Chihara D, Ito H, Matsuda T, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. *Br J Haematol* 2014; **164:** 536–45.

6 Bosetti C, Levi F, Ferlay J, Lucchini F, Negri E, La Vecchia C. Incidence and mortality from non-Hodgkin lymphoma in Europe: the end of an epidemic? *Int J Cancer* 2008; **123:** 1917–23.

7 Clarke, CA, Glaser SL. Changing incidence of non-Hodgkin lymphoma in the United States. *Cancer* 2002; **94:** 2015–23.

8 Van de Schans SA, Issa DE, Visser O, et al. Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989-2007. *Ann Oncol* 2012; **23:** 171–82.

9 Boffetta P. I. Epidemiology of adult non-Hodgkin lymphoma. *Ann Oncol* 2011; **22** (suppl 4)**:** iv27–31.

10 Morton LM, Slager SL, Cerhan JR, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014; **2014:** 130–44.

11 Cerhan, JR, Slager SL. Familial predisposition and genetic risk factors for lymphoma. *Blood* 2015; **126:** 2265–73.

12 Castillo JJ, Ingham RR, Reagan JL, Furman M, Dalia S, Mitri J. Obesity is associate with increase relative risk of diffuse large B-cell lymphoma: a meta-analysis of observational studies. *Clin Lymphoma Myeloma Leuk* 2014; **14:** 122–30.

13 Conde L, Halperin E, Akers NK, et al. Genome-wide association study of follicular lymphoma identifies a risk locus at 6p21.32. *Nat Genet* 2010; **42:** 661–64.

14 Cerhan JR, Berendt S, Vijai J, et al. Genome-wide association study identifies multiple susceptibility loci for diffuse large B-cell lymphoma. *Nat Genet* 2014; **46:** 1233–38.

15 Zhang Y, De Sanjose S, Bracci PM, et al. Personal use of hair dye and the risk of certain subtypes of non-Hodgkin lymphoma. *Am J Epidemiol* 2008; **167:** 1321–31.

16 Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005; **165:** 2337–44.

17 Shiels MS, Ejngels, Linet MS, et al. The epidemic of non-Hodgkin lymphoma in the United States: disentangling the effect of HIV, 1992–2009. *Cancer Epidemiol Biomarkers Prev* 2013; **22:** 1069–78.

18 Bayerdorffer E, Neubauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associate lymphoid tissue type after cure of *Helicobacter pylori* infection. *Lancet* 1995; **345:** 1591–94.

19 Saha A, Robertson ES. Epstein-Barr virus-associate B-cell lymphomas: pathogenesis and clinical outcomes. *Clin Cancer Res* 2011; **17:** 3056–63.

20 Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. *Leukemia* 2005; **19:** 2186–194.

21 Giordano TP, Henderson LH, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA* 2010; **297:** 2010–17.

22 Ferreru AJ, Govi S, Pasini E, et al. *Chlamydophila psittaci* eradication with doxycycline as first-line targets therapy for ocular adnexae lymphoma: final results of an international phase II trial. *J Clin Oncol* 2012; **30:** 2988–94.

23 Colli C, Leinweber B, Mullengger R, Chott A, Ker lH, Cerroni L. *Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. *J Cutan Pathol* 2004; **31:** 232–40.

24 Melenotte C, Million M, Audoly G, et al. B-cell non-Hodgkin lymphoma linked to *Coxiella burnetti*. *Blood* 2016; **127:** 113–21.

25 Chang ET, Canchola AJ, Cockburn M, et al. Adulthood residential ultraviolet radiation, sun sensitivity, dietary vitamin D, and risk of lymphoid malignancies in the California Teachers Study. *Blood* 2011; **118:** 1591–99.

26 Morton LM, Hartge P, Holford TR, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph). *Cancer Epidemiol Biomarkers Prev* 2005; **14:** 925–33.

27 Morton LM, Zheng T, Holford TR, et al. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol* 2005; **6:** 441–536.

28 Wang SS, Flowers CR, Kadin ME, et al. Medical history, lifestyle, family history, and occupational risk factors for peripheral T-cell lymphomas: The InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014; **48:** 66–75.

29 Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; **127:** 2375–90.

30 Basso K, Dalla-Favera R. Germinal centres and B cell lymphomagenesis. *Nat Rev Immunol* 2015; **15:** 172–84.

31 Kridel R, Sehn LH, Gascoyne RD. Pathogenesis of follicular lymphoma. *J Clin Invest* 2012; **122:** 3424–31.

32 Jares P, Colomer D, Campo E. Molecular pathogenesis of mantle cell lymphoma. *J Clin Invest* 2012; **122:** 3416–23.

33 Pasqualucci L, Dalla-Favera R. SnapShot: diffuse large B cell lymphoma. *Cancer Cell* 2014; **25:** 132.

34 de Leval L, Gaulard P. Pathology and biology of peripheral T-cell lymphomas. *Histopathology* 2011; **58:** 49–68.

35 Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood* 2014; **124:** 1473–80.

36 Lenz G, Staudt LM. Aggressive lymphomas. *N Engl J Med* 2010; **362:** 1417–29.

37 Morin RD, Mendez-Lago M, Mungall AJ, et al. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. *Nature* 2011; **476:** 298–303.

38 Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med* 2015; **21:** 922–26.

39 Cheson BD, Risher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32:** 3059–67.

40 Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. *Blood* 2013; **122:** 61–67.

41 Alzahrani M, El-Galaly TC, Hutchings M, et al. The value of routine bone marrow biopsy in patients with diffuse large B-cell lymphoma staged with PET/CT: a Danish-Canadian study. *Ann Oncol* 2016; **27:** 1095–99.

42 The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329:** 987–94.

43 Zhou Z, Sehan LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood* 2014; **123:** 837–42.

44 Solal-Celigny P, Roy P, Colombant P, et al. Follicular lymphoma International Prognostic Index. *Blood* 2004; **104:** 1258–65.

45 Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced stage mantle cell lymphoma. *Blood* 2008; **111:** 558–65.

46 Gutiérrez-García G, García-Herrera A, Cardesa T, et al. Comparison of four prognostic scores in peripheral T-cell lymphoma. *Ann Oncol* 2011; **22:** 397–404.

47 Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol* 2014; **32:** 3048–58.

48 Meignan M, Gallamini A, Haious C. Report of the First International Workshop on interim-PET scan in lymphoma. *Leuk Lymphoma* 2009; **50:** 1257–60.

49 Trotman J, Luminari S, Boussetta S, et al. Prognostic value of PET-CT afteer first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. *Lancet Haematol* 2014; **1:** e17–27.

50 Zelenetz AD, Gordon LI, Wierda WG, et al. Diffuse large B-cell lymphoma version 1.2016. *J Natl Compr Canc Netw* 2016; **14:** 196–231.

51 Mamot C, Klingbiel D, Hitz F, et al. Final results of a prospective evaluation of the predictive value of interim positron emission tomography in patients with diffuse large B-cell lymphoma treated with R-CHOP-14 (SAKK 38/07). *J Clin Oncol* 2015; **33:** 2523–29.

52 Lepretre S, Touzart A, Vermeulin T, et al. Pediatric-like acute lymphoblastic leukemia therapy in adults with lymphoblastic lymphoma: the GRAALL-LYSA LL03 study. *J Clin Oncol* 2015; **34:** 572–80.

53 Coiffier B, Lepage E, Breire J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med* 2002; **346:** 235–42.

54 Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol* 2005; **23:** 5027–33.

55 Récher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. *Lancet* 2011; **378:** 1858–67.

56 Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol* 2008; **26:** 2717–24.

57 Vargo JA, Gill BS, Balasubramani GK, Beriwal S. Treatment selection and survival outcomes in early-stage diffuse large B-cell lymphoma: do we still need consolidative radiotherapy? *J Clin Oncol* 2015; **33:** 3710–17.

58 Ng AK, Dabaja BS, Hoppe RT, Illidge T, Yahalom J. Re-examining the role of radiation therapy for diffuse large B-cell lymphoma in the modern era. *J Clin Oncol* 2016; **34:** 1443–47.

59 Kumar A, Lunning MA, Zhang Z, Miglaiacci JC, Moskowitz CH, Zeleneta AD. Excellent outcomes and lack of prognostic impact of cell of origin for localized diffuse large B-cell lymphoma in the rituximab era. *Br J Haematol* 2015; **171:** 776–83.

60 Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; **403:** 503–11.

61 Wilson WH, Jung SH, Procu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. *Haematologica* 2012; **97:** 758–65.

62 Molina TJ, Canioni D, Copie-Bergman C, et al. Young patients with non-germinal center B-cell-like diffuse large B-cell lymphoma benefit from intensified chemotherapy with ACVBP plus rituximab compared with CHOP plus rituximab: analysis for data from the Groupe d'Etudes des Lymphomes de l'Adulte/Lymphoma Study Association Phase III trial LNH 03-2B. *J Clin Oncol* 2014; **32:** 3996–4003.

63 Nowakowski GS, LaPlant B, Macon WR, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: a phase II study. *J Clin Oncol* 2015; **33:** 251–57.

64 Villa D, Connors JM, Shenkier TN, Gascoyne RD, Sehn LH, Savage KJ. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. *Ann Oncol* 2010; **21:** 1046–52.

65 Bernstein SH, Unger JM, LeBlanc M, Friedberg J, Miller TP, Risher RI. Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 — The Southwest Oncology Group. *J Clin Oncol* 2009; **27:** 114–19.

66 Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood* 2014; **124:** 2354–61.

67 Landsburg DJ, Petrich AM, Abramson JS, et al. Impact of oncogene rearrangement patterns on outcomes in patients with double-hit non-Hodgkin lymphoma. *Cancer* 2016; **122:** 559–64.

68 Cohen JB, Geyer SM, Lozanski G, et al. Complete response to induction therapy in patients with Myc-positive and double-hit non-Hodgkin lymphoma is associated with prolonged progression-free survival. *Cancer* 2014; **120:** 1677–85.

69 Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone. *J Clin Oncol* 2012; **30:** 3460–67.

70 Shipp MA, Harrington DP, Anderson JR, et al. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329:** 987–94.

71 Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 2013; **369:** 1681–90.

72 Muller C, Murawski N, Wiesen MHJ, et al. The roles of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. *Blood* 2012; **119:** 3276–84.

73 Pfreundschuh M, Held G, Zeynalova S, et al. Increased rituximab doses eliminate increased risk and improve outcome of elderly male patients with aggressive CD20+ B-cell lymphomas: the SEXIE-R-CHOP-14 trial of the DSHNHL, abst. 1347. *Haematologica* 2014; **99** (suppl 1)**:** 540 (abstr).

74 Hamlin PA, Portlock CS, Straus DJ, et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. *Br J Haematol* 2005; **130:** 691–99.

75 Savage KH, Yenson PR, Shenkier T, et al. The outcome of primary mediastinal large B-cell lymphoma (PMBCL) in the R-CHOP treatment era. *Blood* 2012; **120:** 303 (abstr).

76 Dunleavy K, Pittaluga S, Maeda LS, et al. Dose adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med* 2013; **368:** 1408–16.

77 Gregory G, Arumugaswamy A, Leung T, et al. Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. *Neuro Oncol* 2013; **15:** 1068–73.

78 Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; **333:** 1540–45.

79 Martín A, Caballero MD. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: influence of prior autologous stem-cell transplantation on outcome. *Haematologica* 2009; **94:** 744.

80 Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28:** 4184–90.

81 Fenske TS, Ahn KW, Graff TM, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. *Br J Haematol* 2016; **174:** 235–48.

82 Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol* 2015; **33:** 540–49.

83 Rosenberg SA. Karnofsky memorial lecture. The low-grade non-Hodgkin's lymphomas: challenges and opportunities. *J Clin Oncol* 1985; **3:** 299–310.

84 Johnson PW, Rohatiner AZ, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol* 1995; **13:** 140–47.

85 Fisher RI, LeBlanc M, Press OW, Maloney DG, Unger JM, Miller TP. New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol* 2005; **22:** 8447–52.

86 Swenson WT, Wooldridge JE, Lynch CF, Forman-Hoffman VL, Chrischilles E, Link BK. Improved survival of follicular lymphoma patients in the United States. *J Clin Oncol* 2005; **23:** 5019–26.

87 Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at the University of Texas M.D., Anderson Cancer Center. *J Clin Oncol* 2006; **24:** 1582–89.

88 Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol* 2015; **33:** 2516–22.

89 MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow up study of patients treated at Stanford University. *J Clin Oncol* 1996; **14:** 1282–90.

90 Armitage JO, Longo DL. Is watch and wait still acceptable for patients with low grade follicular lymphoma? *Blood* 2016; **127:** 2804–08.

91 Zelenetz AD, Gordon LI, Wierda WG, et al. Non-Hodgkin's lymphomas, version 4.2014. *J Natl Compr Canc Netw* 2014; **12:** 1282–303.

92 Ghielmini M, Vitolo U, Kimby E, et al. ESMO guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). *Ann Oncol* 2013; **24:** 561–76.

93 Ardeshna KM, Qian W, Smith P et al. Rituximab versus a watch and wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomized phase 3 trial. *Lancet Oncol* 2014; **15:** 424–35.

94 Rummel MJ, Niederle N, Maschmehyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first line treatment for patients with indolent and mantle-cell lymphomas: an open label, multicenter, randomized, phase 3 non-inferiority trial. *Lancet* 2013; **381:** 1203–10.

95 Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomized controlled trial. *Lancet* 2011; **377:** 42–51.

96 Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). *J Clin Oncol* 2015; **33:** 3635–40.

97 Kothari J, Peggs KS, Bird A, et al. Autologous stem cell transplantation for follicular lymphoma is of most benefit early in the disease course and can result in durable remissions, irrespective of prior rituximab exposure. *Br J Haematol* 2014; **165:** 334–40.

98 Rohatiner AZ, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow up. *J Clin Oncol* 2007; **25:** 2554–59.

99 Khouri IF, McLaughlin P, Saliba PM, et al. Eight year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood* 2008; **111:** 5530–36.

100 Oh DH, Li H, Duan Q, et al. Quantifying benefit of autologous transplantation for relapsed follicular lymphoma patients via instrumental variable analysis. *Biol Blood Marrow Transplant* 2016; **22:** 941–48.

101 Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol* 2013; **31:** 88–94.

102 Davids MS, Seymour JF, Gerecitano JF, et al. Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory non-Hodgkin lymphoma: responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses. *Clin Adv Hematol Oncol* 2014; **12** (8 Suppl 16)**:** 18–19.

103 Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol* 2016; **34:** 2698–704.

104 Chihara D, Cheah CY, Westin JR, et al. Rituximab plus hyper-CVAD alternating with MTX/Ara-C in patients with newly diagnosed mantle cell lymphoma: 15-year follow-up of a phase II study from the MD Anderson Cancer Center. *Br J Haematol* 2016; **172:** 80–88.

105 Cohen JB, Han X, Jemal A, Ward EM, Flowers CR. Deferred therapy is associated with improved overall survival in patients with newly diagnosed mantle cell lymphoma. *Cancer* 2016; **122:** 2356–63.

106 Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol* 2005; **23:** 1984–92.

107 Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle cell lymphoma. *N Engl J Med* 2015; **372:** 944–53.

108 Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood* 2014; **123:** 2944–52.

109 Romaguera JE, Fahyad LE, Feng L, et al. Ten year follow up after intense chemoimmunotherapy with rituximab-hyper CVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol* 2010; **150:** 200–08.

110 Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six year follow up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem cell support: still very long survival but late relapses do occur. *Br J Haematol* 2012; **158:** 355–62.

111 Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment for mantle cell lymphoma. *N Engl J Med* 2015; **373:** 1835–44.

112 Maddocks K, Christian B, Jaglowski S, et al. A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. *Blood* 2012; **125:** 242–48.

113 Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012; **367:** 520–31.

114 Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. *Lancet* 2016; **388:** 565–75.

115 Trneny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomized, multicenter trial. *Lancet Oncol* 2016; **17:** 319–31.

116 Wang ML, Rule S, Martine P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013; **369:** 507–16.

117 Wang WL, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single centre, open label, phase 2 trial. *Lancet Oncol* 2016; **17:** 48–56.

118 Runnel M, Kauser U, Blaser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle cell lymphomas: a multicenter, randomized, open-label, non-inferiority phase 3 trial. *Lancet Oncol* 2016; **17:** 57–66.

119 Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet* 1993; **342:** 575–77.

120 Windisch T, Thiede, C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. *J Clin Oncol* 2016; **23:** 8018–24.

121 Teckie S, Qi S, Lovie S, et al. Long-term outcomes and patterns of relapse of early-stage extranodal marginal zone lymphoma treated with radiation therapy with curative intent. *Int J Radiat Oncol Biol Phys* 2015; **92:** 130–37.

122 Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol* 2005; **23:** 468–73.

123 Kalpadakis C, Pangalis GA, Dimopoulou MN, et al. Rituximab monotherapy is highly effective in splenic marginal zone lymphoma. *Hematol Oncol* 2007; **25:** 127–31.

124 Xing KH, Kahlon A, Skinnider BF, et al. Outcomes in splenic marginal zone lymphoma: analysis of 107 patients treated in British Columbia. *Br J Haematol* 2015; **169:** 520–27.

125 Byrd JC, Jones JJ, Woyach JA, Johnson AJ, Flynn JM. Entering the era of targeted therapy for chronic lymphocytic leukemia: impact on the practicing clinician *J Clin Oncol* 2014; **32:** 3039–47.

126 Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol* 1996; **14:** 925–34.

127 Thomas DA, Cortes J, O'Brien S, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. *J Clin Oncol* 1999; **17:** 2461–70.

128 Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy for filgrastim support for Burkitt or aggressive lymphomas: cancer and leukemia group B study 10002. *Br J Haematol* 2014; **165:** 102–11.

129 Ribrag V, Koscielny S, Bosq J, et al. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomized, controlled, open-label phase 3 trial. *Lancet* 2016; **387:** 2402–11.

130 Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. *N Engl J Med* 2013; **369:** 1915–25.

131 Hoelzer D, Walewski J, Dohner H, et al. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. *Blood* 2014; **124:** 3870–79.

132 Jacobson C, LaCasce A. How I treat Burkitt lymphoma in adults. *Blood* 2014; **124:** 2913–20.

133 Zelenetz AD, Gordon LI, Wierda WG, et al. National Comprehensive Cancer Network, Non-Hodgkin lymphomas, version 4.2014. *J Natl Compre Canc Netw* 2014; **12:** 1282–303.

134 d'Amore F, Gaulard P, Trümper L, et al. Peripheral T-cell lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** (suppl 5)**:** v108–15.

135 Vose JM, Armitage J, Weisenburger D, International T-cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol* 2008; **26:** 4124–30.

136 Herrera AF, Crosby-Thompson A, Friedberg JW, et al. Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network. *Cancer* 2014; **120:** 1993–99.

137 Briski R, Feldman AL, Bailey NG, et al. The role of front-line anthracycline-containing chemotherapy regimens in peripheral T-cell lymphomas. *Blood Cancer J* 2014; **4:** e214.

138 El-Asmar J, Reljic T, Ayala E, et al. Efficacy of high dose therapy and autologous hematopoietic cell transplantation in peripheral T-cell lymphomas as front-line consolidation or in the relapsed/refractory setting: a systematic review/meta-analysis. *Biol Blood Marrow Transplant* 2016; **22:** 802–14.

139 Ellin F, Landstrom J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood* 2014; **124:** 1570–77.

140 Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-cell Lymphoma Project. *Blood* 2008; **111:** 5496–04.

141 Sibon D, Fournier M, Brière J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. *J Clin Oncol* 2012; **30:** 3939–46.

142 Tsai HJ, Lin SF, Chen CC, et al. Long-term results of a phase II trial with frontline concurrent chemoradiotherapy followed by consolidation chemotherapy for localized nasal natural killer/T-cell lymphoma. *Eur J Haematol*. 2015; **94:** 130–37.

143 Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol* 2011; **29:** 4410–16.

144 Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 2012; **30:** 2190–96.

145 Passerini CG, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst* 2014; **106:** djt378.

146 Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. *J Hematol Oncol* 2014; **7:** 11.

147 O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL Study. *J Clin Oncol* 2011; **29:** 1182–89.

148 O'Connor OA, Horwitz S, Maszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. *J Clin Oncol* 2015; **33:** 2492–99.

149 Thompson CA, Ghesquieres H, Maurer MJ, et al. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *J Clin Oncol* 2014; **32:** 3506–12.

150 El-Galaly TC, Jakobsen LH, Hutchings M, et al. Routine imaging for diffuse large B-cell lymphoma in first complete remission does not improve post-treatment survival: a Danish-Swedish population based study. *J Clin Oncol* 2015; **33:** 3993–98.